Heterocyclic Polyfluoro-compounds. Part XXI.[1] Synthesis of Some 2-Substituted Tetrafluoropyridines: 2,3,4,5-Tetrafluoro-6-methoxypyridine and 3,4,5,6-Tetrafluoropyridine-2-carbaldehyde, -2-carboxylic Acid, -2-carboxamide, and -2-carbonitrile

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3,4,5,6-Tetrafluoropyridine-2-carbonitrile and 3,5-dichloro-4,6-difluoropyridine-2-carbonitrile can be obtained by heating 3,4,5,6-tetrachloropyridine-2-carbonitrile with potassium fluoride. Reduction of the tetrafluoro-compound with Raney alloy–aqueous formic acid yields 3,4,5,6-tetrafluoropyridine-2-carbaldehyde (characterised as its oxime), which reacts with oxygen to give 3,4,5,6-tetrafluoropyridine-2-carboxylic acid (perfluoropicolinic acid); acidic hydrolysis of tetrafluoropyridine-2-carbonitrile provides 3,4,5,6-tetrafluoropyridine-2-carboxamide.

Treatment of phenyl 2,3,5,6-tetrafluoropyridyl sulphone with sodium methoxide yields phenyl 2,3,5-trifluoro-6-methoxypyridyl sulphone, which reacts with caesium fluoride in hot tetramethylene sulphone to give 2,3,4,5-tetrafluoro-6-methoxypyridine.

A RANGE of 4-substituted tetrafluoropyridines is available thanks to the regiospecificity of nucleophilic attack on pentafluoropyridine,[2] and the availability of tetrafluoro-3-pyridyl-lithium [3] provides potential access to a variety of 3-substituted tetrafluoropyridines. However, the only route to 2-substituted tetrafluoropyridines developed

[1] Part XX, R. E. Banks, M. G. Barlow, R. N. Haszeldine, and E. Phillips, *J. Chem. Soc.* (*C*), 1971, 1957.

[2] R. E. Banks, 'Fluorocarbons and their Derivatives,' 2nd edn., Macdonald, London, 1970, p. 222; R. E. Banks and M. G. Barlow, 'Fluorocarbon and Related Chemistry,' Chem. Soc. Specialist Periodical Report, 1971, vol. 1, p. 248; R. E. Banks and G. R. Sparkes, *J.C.S. Perkin I*, 1972, 2964.

[3] R. D. Chambers, F. G. Drakesmith, and W. K. R. Musgrave, *J. Chem. Soc.*, 1965, 5045; R. D. Chambers, C. A. Heaton, W. K. R. Musgrave, and I. Chadwick, *J. Chem. Soc.* (*C*), 1969, 1700.

so far,[4,5] *viz.* co-pyrolysis of perfluorocyclohexa-1,3-diene with cyanides (RCN), is restricted to compounds containing highly electronegative substituents (*e.g.* R = Br, CF_3, or C_6F_5). Two other approaches to 2-substituted derivatives are now exemplified: fluorine-for-chlorine exchange in 2-substituted tetrachloropyridines and ' pseudo-protection ' of the 4-fluoro-substituent in pentafluoropyridine from nucleophilic displacement.

An earlier attempt to prepare tetrafluoropyridine-2-carbonitrile was thwarted by the formation of only pentachloropyridine when pyridine-2-carbonitrile was heated with phosphorus pentachloride, a chlorination procedure that worked well when applied to pyridine-4-carbonitrile, giving tetrachloropyridine-4-carbonitrile (71%) and thence, *via* halogen exchange with potassium fluoride, tetrafluoropyridine-4-carbonitrile (71%).[6] The subsequent disclosure [7] of successful chlorination procedures applicable to a number of pyridine derivatives, including pyridinecarbonitriles, has now enabled the sequence to be completed: introduction of a solution of pyridine-2-carbonitrile in carbon tetrachloride into a hot (370—380 °C) tube containing active carbon impregnated with barium chloride and swept with a stream of chlorine provided tetrachloropyridine-2-carbonitrile (39%), which reacted with potassium fluoride at 350—380 °C to give tetrafluoropyridine-2-carbonitrile (max. yield so far 75%), together with 3-chloro-4,5,6- and 5-chloro-3,4,6-trifluoro- and 3,5-dichloro-4,6-difluoro-pyridine-2-carbonitrile.* Treatment of tetrafluoropyridine-2-carbonitrile with 98% sulphuric acid and Raney alloy–aqueous formic acid provided tetrafluoropyridine-2-carboxamide and -2-carbaldehyde, respectively; the aldehyde underwent conversion into the corresponding acid, slowly on contact with air and rapidly when treated with oxygen at 100 °C, and was characterised as its oxime.

The second approach to 2-substituted tetrafluoropyridines arose out of work on 4-substituted tetrafluoropyridines containing sulphur, particularly the synthesis of phenyl 2,3,5,6-tetrafluoropyridyl sulphone (obtainable directly in at least 67% yield from pentafluoropyridine and sodium benzenesulphinate),[8] and knowledge of the mobility of the $PhSO_2$ leaving group in nucleophilic aromatic substitution.[9] Initially, it was shown that treatment of phenyl 2,3,5,6-tetrafluoropyridyl sulphone with caesium fluoride in a hot dipolar aprotic solvent did result in loss of the phenylsulphonyl group with reversion to pentafluoropyridine (*ca.* 20% yield at 80 °C in either tetramethylene sulphone or dimethylformamide after 18 h). The reaction of the sulphone with sodium methoxide in methanol at −20 to 0 °C resulted in preferential displacement of the 2-fluoro-substituent, with formation of phenyl 2,3,5-trifluoro-6-methoxypyridyl sulphone and 2,3,5,6-tetrafluoro-4-methoxypyridine in 65 and 15% yield, respectively; subsequent treatment of the former product with caesium fluoride in tetramethylene sulphone at 113 °C gave 2,3,4,5-tetrafluoro-6-methoxypyridine in 29% yield.

EXPERIMENTAL

I.r., n.m.r., and mass spectra were recorded with a Perkin-Elmer spectrophotometer model 257, a Perkin-Elmer R10 instrument operating at 56·46 and 60 MHz for ^{19}F and ^{1}H spectra, respectively (chemical shifts were measured relative to external trifluoroacetic acid or benzene; values to high field designated positive), and an A.E.I. MS902 spectrometer, respectively.

3,4,5,6-Tetrachloropyridine-2-carbonitrile (Found: C, 30·0; N, 11·75. Calc. for $C_6Cl_4N_2$: C, 29·75; N, 11·6%), m.p. 147—148 °C, was prepared (by P. R. LEYTHAM) in 39% yield by direct chlorination of pyridine-2-carbonitrile at 370—380 °C in the presence of activated carbon impregnated with barium chloride.[7]

3,4,5,6-*Tetrafluoropyridine-2-carbonitrile*.—A carefully dried, intimate mixture of finely ground 3,4,5,6-tetrachloropyridine-2-carbonitrile (18·7 g, 77·3 mmol) and powdered potassium fluoride (100 g, 1·72 mol) was heated in the absence of air at 560 °C for 14 h in a mild steel tube of the type described previously.[10] Distillation of the volatile product gave 3,4,5,6-*tetrafluoropyridine-2-carbonitrile* (4·17 g, 23·7 mmol, 31%) (Found: C, 41·1; N, 15·8. $C_6F_4N_2$ requires C, 40·9; N, 15·9%), b.p. 97 °C at 64 mmHg, $\lambda_{max.}$ 4·44 μm (C≡N str.), δ_F (neat liquid; the spectrum approximates to that of an ABPX system in which two of the nuclei, 3-F and 4-F, are strongly coupled) +3·2 (6-F), +59·0 (3- and 4-F; $\nu_4 - \nu_3 = 22·1$ Hz), and +70·3 (5-F) p.p.m. ($|J_{3,4}|$ 18·2, $J_{3,5}$ ±11·6, $J_{3,6}$ ±23·9, $J_{4,5}$ ∓17·6, $J_{4,6}$ ±19·9, $J_{5,6}$ ∓23·5 Hz), *m/e* 176 ($M^{+\cdot}$, 100%), 131 [$(M - FCN)^{+\cdot}$, 11], and 124 [$(M - C_2N_2)^{+\cdot}$, 6]. A much higher yield of this product (75%) was obtained by heating 50 g (0·21 mol) of tetrachloropyridine-2-carbonitrile with 200 g (3·45 mol) of anhydrous potassium fluoride at 380 °C for 21 h.

Distillation of the volatile product from a similar reaction between 21·5 g (88·9 mmol) of tetrachloropyridine-2-carbonitrile and 75 g (1·3 mol) of potassium fluoride at 350 °C for 18 h provided tetrafluoropyridine-2-carbonitrile (1·27 g, 7·22 mmol, 8%), an intermediate fraction (6·13 g) that was shown by ^{19}F n.m.r. spectroscopy to be a *ca.* 2 : 1 mixture of 3-chloro-4,5,6-trifluoropyridine-2-carbonitrile [δ_F +2·3br (6-F), +37·8 (4-F), and +73·5 (5-F) p.p.m.] and 5-chloro-3,4,6-trifluoropyridine-2-carbonitrile [δ_F −11·7 (6-F), +37·8 (4-F), and +61·7 (3-F) p.p.m.], and 3,5-*dichloro-4,6-difluoropyridine-2-carbonitrile* (5·35 g, 25·6 mmol, 29%) (Found:

* Since this work was completed (see F. E. Rickett, Ph.D. Thesis, Manchester, 1969), an account has appeared in the patent literature (F. E. Torba, Ger. Offen., 1,816,685/1969) of the preparation of chlorofluoropyridine-2-, -3-, and -4-carbonitriles *via* treatment of the corresponding tetrachloro-compounds with potassium fluoride. The 3,5-dichloro-4,6-difluoropyridine-2-carbonitrile isolated possessed m.p. 61·8—66·5 °C.

[4] L. P. Anderson, W. J. Feast, and W. K. R. Musgrave, *J. Chem. Soc.* (*C*), 1969, 2559.

[5] See R. E. Banks, K. Mullen, W. J. Nicholson, C. Oppenheim, and A. Prakash, *J.C.S. Perkin I*, 1972, 1098, for an outline of a route currently undergoing investigation.

[6] R. E. Banks, R. N. Haszeldine, and I. M. Young, *J. Chem. Soc.* (*C*), 1967, 2089.

[7] R. M. Bimber, U.S.P. 3,325,503/1967; W. H. Taplin, U.S.P. 3,420,833/1969.

[8] R. E. Banks, R. N. Haszeldine, D. R. Karsa, F. E. Rickett, and I. M. Young, *J. Chem. Soc.* (*C*), 1969, 1660.

[9] See, for example, J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, Amsterdam, London, and New York, 1968, p. 166; D. J. Brown and P. W. Ford, *J. Chem. Soc.* (*C*), 1967, 568 (note that these investigators failed to obtain 2-fluoropyrimidine *via* reaction of methyl 2-pyrimidyl sulphone with sodium fluoride in dimethyl sulphoxide).

[10] R. E. Banks, D. S. Field, and R. N. Haszeldine, *J. Chem. Soc.* (*C*), 1967, 1822.

C, 34·2; N, 13·3. $C_6Cl_2F_2N_2$ requires C, 34·45; N, 13·4%), m.p. 63—66 °C, $\lambda_{max.}$ 4·44 μm (C≡N str.), δ_F (*ca.* 50% in CCl_4) −14·2br (d, 6-F) and +15·2 (d, $|J|$ 19 Hz, 4-F) p.p.m. (rel. int. 1 : 1).

3,4,5,6-*Tetrafluoropyridine-2-carbaldehyde*.—Treatment of tetrafluoropyridine-2-carbonitrile (1·81 g, 10·3 mmol) with Raney alloy (50 : 50, 3·32 g) in hot 75% (v/v) aqueous formic acid (50 cm³) as described for the conversion of tetrafluoropyridine-4-carbonitrile into the corresponding aldehyde [6] gave 3,4,5,6-tetrafluoropyridine-2-carbaldehyde (0·75 g, 4·19 mmol, 41%), b.p. 80 °C at 31 mmHg, $\lambda_{max.}$ 5·78 μm (C=O str.). A solution of the aldehyde (0·55 g, 3·07 mmol) in ethanol (2 cm³) was shaken with a solution of hydroxylamine hydrochloride (0·5 g) and sodium acetate (0·5 g) in water (5 cm³) at 21 °C for 30 min; sublimation of the solid that precipitated afforded (at <1 mmHg and bath temp. 60 °C) the *oxime* (0·41 g, 2·11 mmol, 69%) (Found: C, 37·0; H, 1·1; N, 14·3. $C_6H_2F_4N_2O$ requires C, 37·1; H, 1·0; N, 14·4%), m.p. 115 °C, δ_F (25% in hexamethylphosphoramide) +7·15 (6-F), +62·8 (4- or 5-F), +67·4 (5- or 4-F), and +81·8 (3-F) p.p.m., δ_H (same soln.) −1·2 (s, C*H*:NOH) and −6·8br (s, CH:NO*H*).

3,4,5,6-*Tetrafluoropyridine-2-carboxamide*.— Tetrafluoropyridine-2-carbonitrile (2·30 g, 13·1 mmol) was heated with 98% sulphuric acid (25 cm³) at 130 °C for 3 h. The product was poured into ice–water (200 cm³) and the solid that precipitated was sublimed, *in vacuo*, to yield the *amide* (2·21 g, 11·4 mmol, 87%) (Found: C, 37·2; H, 1·3; F, 38·8; N, 13·9. $C_6H_2F_4N_2O$ requires C, 37·1; H, 1·0; F, 39·2; N, 14·4%), m.p. 124—125 °C, $\lambda_{max.}$ (mull) 2·91, 3·03 (free N-H str.), 3·11 (H-bonded N–H str.), 5·93 (C=O str.), 6·02 (H-bonded C=O str.), 6·14 (H-bonded N–H def.), and 6·21 (free N–H def.) μm.

3,4,5,6-*Tetrafluoropyridine-2-carboxylic Acid*.—A fine stream of oxygen was passed through tetrafluoropyridine-2-carbaldehyde (1·51 g, 7·95 mmol) at 100 °C for 1·75 h. Sublimation of the solid product at <1 mmHg and 80 °C yielded the acid (0·84 g, 3·91 mmol, 51·5%), m.p. 95—96 °C, $\lambda_{max.}$ (mull) 3·0—4·0 (O–H str.) and 5·78 and 5·86 (d, C=O str.) μm.

2,3,4,5-*Tetrafluoro-6-methoxypyridine*.—A solution of sodium methoxide (1·17 g, 21·6 mmol) in methanol (5 cm³) was added dropwise to a cold (−20 °C) stirred solution of phenyl 2,3,5,6-tetrafluoropyridyl sulphone [8] (5·02 g, 17·2 mmol) in tetrahydrofuran (25 cm³). The mixture was warmed to 0 °C, stirred for 1 h, then poured into ice-cold 1M-hydrochloric acid (500 cm³). The white solid that precipitated was washed with water and crystallised from ethanol to yield *phenyl 2,3,5-trifluoro-6-methoxypyridyl sulphone* (2·71 g, 8·96 mmol, 52%) (Found: C, 47·8; H, 2·6; N, 4·5; S, 10·8. $C_{12}H_8F_3NO_3S$ requires C, 47·5; H, 2·6; N, 4·6; S, 10·6%), white needles, m.p. 125—127 °C, δ_F (*ca.* 30% in Me_2CO) +14·8 ($|J_{2.3}|$ 24·2, $|J_{2.5}|$ 32·2 Hz, 2-F), +60·7 (5-F), and +74·5 ($|J_{3.5}|$ 9·1 Hz, 3-F) p.p.m. (rel int. 1 : 1 : 1). The aqueous solution was extracted with ether (4 × 50 cm³), and the extract, combined with the mother liquor from the crystallisation of the foregoing product, was dried ($MgSO_4$) and distilled, to give 2,3,5,6-tetrafluoro-4-methoxypyridine (0·48 g, 2·65 mmol, 15%) (Found: C, 39·8; H, 1·7; N, 7·6%; $M^{+\cdot}$, 181. Calc. for $C_6H_3F_4NO$: C, 39·8; H, 1·65; N, 7·7%; *M*, 181), possessing the same i.r. spectrum as an authentic specimen; [11] crystallisation of the distillation residue from ethanol afforded more phenyl 2,3,5-trifluoro-6-methoxypyridyl sulphone (0·68 g, 2·24 mmol, total yield 65%).

A mixture of phenyl 2,3,5-trifluoro-6-methoxypyridyl sulphone (1·39 g, 4·59 mmol), caesium fluoride (5·0 g, 33 mmol), and tetramethylene sulphone (20 cm³) was heated at 113 °C for 24 h in the absence of air in a Pyrex ampoule (200 cm³). The product was worked up by a combination of distillation and g.l.c. techniques to provide 2,3,4,5-*tetrafluoro-6-methoxypyridine* (0·24 g, 1·33 mmol, 29%) (Found: C, 39·8; H, 1·8; N, 7·5%; $M^{+\cdot}$, 181. $C_6H_3F_4NO$ requires C, 39·8; H, 1·65; N, 7·7%; *M*, 181), a colourless liquid, δ_F +12·7br (structureless, 2-F), +62·4 ($|J_{2.4}|$ 12, $|J_{4.5}|$ 17, $|J_{3.4}|$ 19 Hz, 4-F), +85·7 ($|J_{3.5}|$ 3, $|J_{2.5}|$ 24 Hz, 5-F), and +93·2 ($|J_{2.3}|$ 19 Hz, 3-F) p.p.m. (rel. int. 1 : 1 : 1 : 1).

We thank Dr. M. G. Barlow for a report on the ^{19}F n.m.r. spectrum of tetrafluoropyridine-2-carbonitrile.

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[11] R. E. Banks, J. E. Burgess, W. M. Cheng, and R. N. Haszeldine, *J. Chem. Soc.*, 1965, 575.